Late computed tomography scan response improvement and gallium scintigraphy evaluation as on-treatment prognostic parameters to tailor treatment intensity in patients with Hodgkin’s lymphoma. A prospective phase II study

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Background: Tailoring treatment intensity is critical in Hodgkin’s lymphoma (HL). Ongoing prognostic parameters may be an useful adjunct to pretreatment stratification. We used the kinetics of computed tomography (CT) scan response and residual gallium (Ga)-67 uptake to better stratify risk.

Materials and methods: Patients received 4–8 adriamycin, bleomycin, vinblastine and dacarbazine courses according to stage. Disease was reassessed evaluating late computed tomography scan response improvement (CTRI) and Ga-67 uptake. Patients received no further treatment, radiotherapy (RT) or additional chemotherapy + RT according to the presence of none (low risk), one (intermediate risk) and both parameters (high risk). Patients with bulky mediastinum received RT anyhow.

Results: Among 102 assessable patients, 35 showed late CTRI and 9 residual Ga-67 uptake. In 30 patients with bulky mediastinum, the 3-year progression-free survival (PFS) was significantly better when neither parameter was present (100% versus 69%; \( P = 0.02 \)). In 72 patients without bulky mediastinum, treatment was tailored according to risk assignment. Relapses occurred in 5 of 47 low-risk and 3 of 21 intermediate-risk patients, with no differences between the two groups, and in 3 of 4 high-risk patients.

Conclusion: This study shows that two on-treatment parameters, late CTRI and residual Ga-67 uptake, can predict PFS in HL and identify patients in which RT can be spared without apparently affecting the outcome.

Key words: computed tomography scan, Ga-67 scintigraphy, Hodgkin’s lymphoma, prognostic factors

introduction

The outcome of patients with Hodgkin’s lymphoma (HL) has improved dramatically over the last decades. A long-term survival rate of >80% is achievable with combination chemotherapy and radiotherapy (RT) [1]. As follow-up, however, became longer, serious long-term adverse effects of treatment, such as heart and lung disease and secondary malignancies, became evident causing a significant excess mortality [2–4]. Therefore, tailoring treatment intensity to the individual patient has become critical to achieve the highest cure rate with the least morbidity and mortality.

Ann Arbor stage of disease and B symptoms at presentation remain the major determinants for patients stratification; together with several pretreatment prognostic factors, such as erythrocyte sedimentation rate (ESR), bulky disease, age, extranodal disease and number of involved regions, they are commonly used to assign patients to different treatment programs [1, 5]. Diagnostic parameters at diagnosis, however, do not accurately predict the actual sensitivity of the tumor to treatment and significant discrepancies exist in the outcome of patients belonging to the same prognostic groups and receiving the same treatment. In fact, responsiveness to treatment is the most important predictor of outcome in HL, with patients achieving a complete remission (CR) having the best prognosis [6–9]. Response assessment is commonly carried out at the end of treatment on the basis of conventional morphological methods, such as computed tomography (CT) scan or functional imaging methods [10–13].
Recently, ‘on-treatment’ evaluation of response has been proposed to better predict the outcome. Strong evidence has been accumulating that early assessment of response after one to two cycles of chemotherapy, particularly with metabolic imaging methods such as gallium (Ga)-67 scintigraphy and, more recently, positron emission tomography with 2-[fluorine-18]fluoro-2-deoxy-d-glucose (FDG–PET), can identify patients at poor prognosis, in whom an early treatment intensification may be warranted [13–18]. On the other hand, the chance to safely reduce treatment duration or intensity relying on ongoing response parameters has been less studied. In this article, we present the results of a single-center phase II study, in which the kinetics of CT response in the late phase of chemotherapy and the result of postchemotherapy Ga-67 scintigraphy have been respectively used as prognostic parameters to tailor the intensity of up-front treatment in HL patients, avoiding RT in those considered at low risk or prolonging chemotherapy before RT in those considered at high risk of active disease persistance.

materials and methods

patients

All HIV-negative patients diagnosed with HL were eligible for the study, if they had <80 years and no organ deficiency or any other conditions that excluded them from a standard dose treatment strategy. Patients with favorable Ann Arbor stage I A (single node of HL with all of lymphocyte predominant or nodular sclerosis histology, bulk <3 cm, ESR <50 mm/h, disease involving high neck or epitracheal region only) were excluded and received RT only. In every case, the diagnosis of HL was on the basis of the analysis of histological samples obtained by lymphoadenectomy or needle core biopsy and supported by appropriate immunophenotypic analysis, with evaluation of CD3, CD20, CD15 and CD30 and, when required, PAX5, ALK1 and CD45RB antigen expression [19]. All patients gave an informed consent according to the Declaration of Helsinki.

initial staging

Staging procedures included physical examination, Waldeyer’s ring evaluation, thorax X-rays, CT scan of chest, abdomen and pelvis, bone marrow biopsy, Ga-67 scintigraphy and further test when clinically indicated. The following clinical data at diagnosis were obtained: gender, age, Ann Arbor stage, number of involved regions, extranodal involvement, presence of B symptoms, bulky disease (tumor >10 cm and/or mediastinal bulk >1/3 of thoracic diameter) and International Prognostic Score (IPS) [20].

Patients were stratified into three subgroups: clinical stage I–II A without bulky mediastinal masses were classified as ‘early stage’, stage I–II with B symptoms and/or with bulky mediastinal mass or stage III A as ‘intermediate stage’ and stage III B–IV as ‘advanced stage’.

treatment strategy

Standard chemotherapy was the ABVD regimen (adriamycin, bleomycin, vinblastine and dacarbazine) given for four, six and eight courses to early-stage, intermediate-stage and advanced-stage patients, respectively.

A first response assessment was carried out by CT scan two cycles before the end of planned chemotherapy. Patients with progressive disease or less than partial remission (PR) were considered off study. At the end of chemotherapy, a further CT scan and a Ga-67 scintigraphy were carried out. Residual Ga uptake at a previous site of disease was considered a “residual Ga-67 positivity”. An improvement between the two CT scan before and after the last two CT cycles, defined as >10% decrease in the sum of the products of the greatest diameters of the measurable disease, was considered as late ‘computed tomography scan response improvement’ (CTRI). Response to treatment was defined according to guidelines developed by the International Workshop on Response Criteria for non-HL [21].

Residual Ga-67 positivity and ‘late CTRI’ were used as prognostic parameters to tailor treatment intensity. Patients received involved-field RT at the end of chemotherapy only when they showed either residual Ga-67 positivity or late CTRI, whereas RT was avoided in the absence of both parameters, with the aim to avoid long-term toxicity without increasing the risk of relapse. Patients with both residual Ga-67 positivity and late CTRI were given two additional courses of ABVD and RT. Patients with bulky mediastinum received RT in any case and the ability of the two prognostic parameters to predict their relapse rate was evaluated retrospectively.

Involved-field RT was given with 30–36 Gy with a boost of 4–10 Gy to the sites of residual disease or to the sites of initially bulky disease in daily fractions of 2 Gy.

Ga-67 scintigraphy

Ga scans were carried out 48–72 h after i.v. injection of 185–200 MBq of $^{67}$Ga citrate with total body scan associated to single positron emission computed tomography imaging for certain regions of clinical interest, with subsequent axial, coronal and sagittal reconstruction of tomographic images.

statistical analysis

Clinical features at diagnosis were compared between patients classified as ‘low risk’ and intermediate risk using unpaired t-test and Fisher’s exact test for continuous or categorical variables. Overall survival (OS) was calculated from the date of diagnosis to death or the last time the patient was seen and progression-free survival (PFS) from the date of diagnosis until progression or relapse or the last time the patient was known to be disease free and alive. OS and PFS were estimated using the Kaplan–Meier method and differences between subgroups were tested with the log-rank test. Multivariate Cox regression analyses were applied to evaluate baseline characteristics (age < or ≥30 years, stage I–II versus III–IV, B symptoms, extranodal disease, bulky disease, IPS 0–2 versus >2) and late CTRI and residual Ga-67 positivity for the prediction of PFS.

results

From January 1999 until June 2004, 110 consecutive patients entered the study. Median age was 31 years (14–79). Thirty-nine patients belonged to the early stage, 41 to the intermediate-stage and 30 to the advanced-stage group.

One hundred and two patients (92.7%) were assessable for disease reassessment according to the strategy of the study: 38 early stage (11 Ann Arbor stage I A; 27 stage II A), 37 intermediate stage (9 stage II A and bulky mediastinum; 22 stage II B, including 11 with bulky mediastinum; 6 stage III A) and 27 advanced stage (8 stage III B, including 3 with bulky mediastinum; 19 stage IV, including 7 with bulky mediastinum). Causes of exclusion included poor tolerance to chemotherapy in a 74-year-old early-stage patient and early disease progression in four patients (three intermediate-stage patients and one advanced-stage patient); three patients were treated in other centers. The characteristics of 102 patients assessable for the study are summarized in Table 1.
risk stratification according to late CTRI and Ga-67 scintigraphy

The two prognostic parameters, late CTRI and residual Ga-67 positivity, were absent in 63 (16 with and 47 without bulky mediastinal mass) of 102 patients (62%) defined as low risk. One of the two parameters was present in 34 (13 with and 21 without bulky mediastinal mass) of 102 patients (33%) defined as intermediate risk. In 5 (one with and four without bulky mediastinal mass) of 102 patients (5%) defined as ‘high risk’, both prognostic parameters were positive.

treatment assignment and outcome

bulky mediastinum. Thirty patients had bulky mediastinal mass and received RT irrespective of risk assessment. Eleven patients obtained CR, 15 unconfirmed CR (CRu) and 4 PR.

According to late CTRI and residual Ga-67 positivity, 16 patients (53%) had low-risk disease (8 of 20 with intermediate and 8 of 10 with advanced-stage disease); they are alive and progression free. Of 13 (43%) intermediate-risk patients (11 of 20 with intermediate and 2 of 10 with advanced-stage disease), three relapsed after 9, 10 and 18 months. One patient (3%) with intermediate stage had high-risk disease had disease progression 1 month after receiving two additional cycles of ABVD plus RT. After a median follow-up of 38.5 months (range 12–76), the 3-year PFS was 86%. It was significantly higher in low-risk compared with intermediate- and high-risk patients (100% versus 69%; P = 0.02) (Figure 1). PFS was significantly different also comparing low-risk patients versus intermediate-risk patients only (100% versus 74.6%; P = 0.04).

nonbulky mediastinum. Seventy-two patients without bulky mediastinal mass were treated according to late CTRI and residual Ga-67 positivity. Forty-seven patients (65%) had low-risk disease (23 of 38 in early, 9 of 17 in intermediate and 15 of 17 in advanced stage) and stopped treatment; 21 (29%) had intermediate-risk disease (12 of 38 in early, 7 of 17 in intermediate and 2 of 17 in advanced stage) and received RT; 4 (5%) had high-risk disease (3 of 38 in early and 1 of 17 in intermediate stage) and were planned to receive additional chemotherapy + RT. At the end of the treatment program, the CR rate was 65%, CRu 28% and PR 4%. Two of four high-risk patients (50%) had disease progression early after initial response, while receiving the two planned additional cycles of ABVD. Nine patients relapsed. Overall, after a median follow-up of 31 months (range 11–75), the 3-year PFS was 84%. Table 2 summarizes the frequency of relapse/progression both according to on-treatment risk-group assignment and disease stage at diagnosis. The frequency of disease relapse or progression did not differ according to initial disease stage. Specifically, according to risk assessment, relapses occurred in five low-risk patients (10.6%) after 3, 7, 8, 32 and 42 months and in three intermediate-risk patients (14%) after 4, 9 and 19 months, with no significant differences between the two groups. Treatment failed in three of four high-risk patients (75%) (two early progression and one relapse 14 months after CR). PFS according to risk group is shown in Figure 2.

All the above analyses were carried out on an intention-to-treat basis. Treatment violations included two patients with bulky mediastinum and stage IV disease who did not receive RT, three low-risk patients who actually received RT because of patient’s decision and three intermediate-risk patients without bulky mediastinum who did not receive RT because of lung toxicity after chemotherapy (two patients) and patient’s wish (one patient). Excluding from the analysis patients with treatment violations, the 3-year PFS for patients with bulky

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**Table 1.** Pretherapy characteristics of patients assessable for the study (N = 102)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>N = 72 Nonbulky disease</th>
<th>N = 30 Medialstinal bulky</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>32 (14–79)</td>
<td>29 (15–56)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (40%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Female</td>
<td>43 (60%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11 (15%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>II</td>
<td>38 (53%)</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>III</td>
<td>11 (15%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>IV</td>
<td>12 (17%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (21%)</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>No</td>
<td>57 (79%)</td>
<td>22 (73%)</td>
</tr>
<tr>
<td>B symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (32%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>No</td>
<td>49 (68%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodular lymphocyte pred</td>
<td>6 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Classical</td>
<td>66 (92%)</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>Lymphocyte rich</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>39 (54%)</td>
<td>26 (87%)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>12 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Not further classifiable</td>
<td>14 (19%)</td>
<td>4 (13%)</td>
</tr>
</tbody>
</table>

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*Most patients in this group had diagnosis made on core needle biopsy, especially obtained from mediastinum or retroperitoneum.

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Figure 1. Progression-free survival of patients with bulky mediastinal mass according to ‘risk group’ (see text for definition of risk) (N = 30).
mediastinal masses was 100% in low-risk compared with 69% in intermediate- and high-risk patients (P = 0.03) and for patients without bulky mediastinal disease it was 92% compared with 88% in intermediate-risk patients (P = 0.57).

analysis of prognostic parameters

Analysing patients’ clinical features at diagnosis, no significant differences were found in the most commonly used prognostic factors between patients classified as low risk and intermediate risk or high risk according to late CTRI and residual Ga-67 positivity, both in patients with or without bulky mediastinum. Table 3 shows a comparison between low risk and intermediate risk. The five patients with high-risk disease were in stage I A (two patients), stage II A and stage II B (two patients; one with bulky mediastinum); their median age was 33 years (range 15–60).

The strength and independence of late CTRI and residual Ga-67 positivity as prognostic factors was further confirmed by multivariate analysis including established prognostic factors at diagnosis, which indicated PFS to be significantly related to late CTRI (P = 0.002) and Ga-67 positivity (P = 0.004).

When considering the relative contribution to risk stratification of the two prognostic parameters of the study, late CTRI was present in 35 of 102 (34.3%) patients [15 of 38 (39%) early stage, 17 of 37 (46%) intermediate stage and 3 of 27 (11%) advanced stage] and residual Ga-67 positivity in 9 (9%) patients [3 of 38 (8%) early stage, 5 of 37 (13%) intermediate stage and 1 of 27 (4%) advanced stage]. There were no significant differences in their ability to predict subsequent relapse/progression (Figure 3). More specifically, the assignment to intermediate-risk group was made according to late CTRI in 30 of 34 patients (88%) and residual Ga-67 positivity in 4 of 34 patients (12%).

Considering the usual approach to HL, without mediastinal bulky disease, where complementary RT is commonly used in all early- and intermediate-stage patients and in advanced-stage patients not achieving CR after CT, our strategy allowed us to save RT in 40 of 72 patients (55%); 23 of 38 in the early, 9 of 17 in the intermediate and 8 of 17 in the advanced-stage group.

overall treatment results and secondary tumors

Considering the whole series of 110 patients, 107 are assessable for treatment response; 59 of 107 had CR, 35 of 107 CRu, 7 of 107 PR and 6 of 107 disease progression. The OS rate was 97% at 3 years, with a 3-years PFS of 82%, after a median follow-up of 36 months (range 3–76). Three-years OS and PFS were, respectively, 100% and 84% in early-stage, 95% and 76% in intermediate-stage and 96% and 88% in advanced-stage patients. Thirteen of 15 patients with relapse/progression received high-dose therapy and autologous stem-cell transplantation and 10 achieved a second CR and one PR. One patient in the low-risk group developed a diffuse large-cell non-HL 3 months after CR and one in the high-risk group a larynx carcinoma 26 months after the end of first-line treatment, while in second CR.

discussion

The balance between treatment intensity and late toxicity is critical for HL. Treatment strategy has been traditionally tailored according to pretreatment prognostic parameters [1, 5]. CR duration and long-term outcome, however, might be more affected by tumor chemosensitivity than factors at presentation. Recently, metabolic imaging methods such as Ga-67 scintigraphy and FDG–PET proved useful to accurate initial staging and evaluation after treatment. Relying on the detection of metabolic alterations in cancer cells, these methods yield more information compared with the traditional CT scan. Particularly, PET has been increasingly used in the management of lymphoma patients in combination with or even instead of CT scan [22]. In the present study, which started when PET was not widely available, we used Ga-67 scintigraphy, which maintains a similar significance albeit with some disadvantages compared with PET [23, 24].

Moreover, Ga-67 scintigraphy and PET can predict outcome, identifying patients with the same disease stages at diagnosis but different kinetics of response [13–18]. Notably, the relatively small subgroup of patients (20%), who had residual active disease after two cycles of chemotherapy, had a worse prognosis and could be candidate to early treatment intensification [18].

On the other hand, early identification of patients showing good response could theoretically allow to reduce treatment...
Table 3. Distribution of prognostic factors at diagnosis according to risk group

<table>
<thead>
<tr>
<th></th>
<th>Nonbulky disease</th>
<th>Mediastinal bulky</th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low risk</td>
<td>Intermediate risk</td>
<td>Low risk</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>Age ≥50 years</td>
<td>11/47 (23.4%)</td>
<td>5/21 (23.8%)</td>
<td>1/16 (6.2%)</td>
<td>1/13 (7.6%)</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>32 (16–79)</td>
<td>30 (14–70)</td>
<td>32 (17–56)</td>
<td>29 (16–56)</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>27/20</td>
<td>11/10</td>
<td>5/11</td>
<td>7/6</td>
</tr>
<tr>
<td>Stage III–IV</td>
<td>17/47 (36.1%)</td>
<td>6/21 (28.5%)</td>
<td>8/16 (50%)</td>
<td>2/13 (15.3%)</td>
</tr>
<tr>
<td>B symptoms</td>
<td>17/47 (36.1%)</td>
<td>5/21 (23.8%)</td>
<td>9/16 (56.2%)</td>
<td>7/13 (53.8%)</td>
</tr>
<tr>
<td>ESR ≥50 mm/h</td>
<td>16/47 (34%)</td>
<td>7/21 (33.3%)</td>
<td>8/16 (50%)</td>
<td>6/13 (46.1%)</td>
</tr>
<tr>
<td>≥3 involved regions</td>
<td>20/47 (42.5%)</td>
<td>7/21 (33.3%)</td>
<td>8/16 (50%)</td>
<td>7/13 (53.8%)</td>
</tr>
<tr>
<td>≥4 involved regions</td>
<td>13/47 (27.6%)</td>
<td>5/21 (23.8%)</td>
<td>2/16 (12.3%)</td>
<td>3/13 (23.0%)</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td>13/47 (27.6%)</td>
<td>2/21 (9.5%)</td>
<td>6/16 (37.5%)</td>
<td>2/13 (15.3%)</td>
</tr>
<tr>
<td>IPS (mean)</td>
<td>1.5</td>
<td>1.4</td>
<td>2.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*Low-risk* and ‘intermediate-risk’ groups are compared, both in patients with and without bulky mediastinum. Differences are not statistically significant. ESR, erythrocyte sedimentation rate; IPS, International Prognostic Score.

Figure 3. Comparison of progression-free survival of patients with computed tomography scan response improvement (CTRI) and residual gallium positivity.

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Intensity, thereby minimizing its side-effects. Particularly, safely avoidance of RT would be desirable to reduce the risks of late cardiotoxicity and secondary neoplasms. Several controlled studies are evaluating the possibility to reduce RT, randomizing patients between programs including or not RT, as well as different RT doses and irradiation fields [25–28]. The present study shows that two on-treatment prognostic parameters, late CTRI and residual Ga-67 uptake, analyzed before RT, can predict PFS and identify patients who can save part of treatment without compromising its overall result.

Both CT scan and Ga-67 scintigraphy have been extensively used after treatment to assess the degree of response and to predict recurrence risk. While residual Ga-67 uptake is associated with high risk of early recurrence [10–13], post-treatment CT scan does not allow to differentiate between a benign fibrotic mass and residual tumor. The stability of CT scan response during follow-up, however, is concordantly considered an hallmark of disease eradication, even in patients with measurable residual masses, and correlates with low risk of relapse [7, 29].

In this study, the evaluation of CT scan stability was anticipated during chemotherapy and proved to be a powerful prognostic parameter as well. Improvement in the degree of CT scan response, defined as late CTRI, was observed in 34% of patients, more frequently than residual Ga-67 uptake, which was demonstrated in 9%. Both parameters showed a comparable negative effect on PFS. In the subgroup of patients with bulky mediastinum, who received a uniform treatment program, the presence of at least one parameter was sufficient to significantly worsen PFS. Of note, neither late CTRI nor residual Ga-67 uptake correlated with any of the pretreatment parameters which usually predict HL prognosis, including stage at diagnosis. In HL patients without bulky mediastinum, both the need and the optimal doses and radiation fields of RT in early or intermediate stage at diagnosis are currently analyzed in prospective randomized trials [25, 26]. Also, in advanced-stage patients, the intensity of CT and the role of RT are the subject of ongoing studies [30–33]. In this study, late CTRI and residual Ga-67 uptake were prospectively used to tailor treatment strategy. Of note, the distribution of patients among the three risk groups identified by the presence of none low risk, one intermediate risk or both parameters high risk did not correlate with their disease stage at diagnosis (Table 2). For example, no advanced-stage patient was classified in the high-risk subgroup as opposed to 8% of early stage. Late CTRI could be theoretically expected more frequently in patients with early stages where CT scans are carried out after two and four cycles of ABVD. In our study, intermediate-stage patients undergoing CT scans after four and six cycles, however, had similar frequencies of late CTRI (39% and 46%, respectively).

In patients without late CTRI and residual Ga-67 uptake after CT considered at low risk of HL recurrence, RT was actually spared and treatment was concluded after the planned chemotherapy. These patients could not be identified by any pretreatment characteristics. They, however, represented more than half of patients without bulky mediastinum in our series, i.e. a quite large subgroup of patients, for which further follow-up will tell if the goal of reducing late RT-related cardiovascular events and second neoplasms will be achieved. The reduced treatment intensity in this subgroup of patients did not apparently translate in a worse outcome compared with the
subgroup receiving RT. Their relapse rate was not different than expected for patients in similar disease stages treated with a combination of CT and RT [26, 32] and OS of the entire series was also in line with that of published series of HL patients [1].

The adverse prognosis in the presence of late CTRI and residual Ga-67 uptake was best demonstrated by the 3% of patients identified as at high risk by their simultaneous presence, who actually had a very dismal prognosis, with a relapse rate of 75%, even though they had early or intermediate-stage disease at diagnosis. Moreover, relapses occurred in spite of consolidation RT and treatment intensification by further chemotherapy. We believe that in this subset of patients further treatment intensification with high-dose therapy and stem-cell support early during remission should be strongly considered, preferably after active HL is demonstrated by biopsy.

These observations confirm that pretreatment prognostic evaluation in HL does not allow to fully predict the outcome of the single patient and that on-treatment prognostic assessment, with FDG–PET or other parameters including those used in this study, may significantly improve our ability to predict his disease course. However, since these parameters are evaluable after treatment, they are not applicable at those patients who do not complete the treatment program because of early disease progression or poor treatment tolerance.

The analysis of CT scan response kinetics, which has not been widely used so far, allowed the identification of more than one-third of nonbulky HL patients as at risk of recurrence. Since it did not fully correlate with the presence of residual Ga-67 uptake, we believe that its evaluation deserves to be extended and validated in larger cohorts of patients as a simple and relatively inexpensive prognostic indicator for management of HL patients. Given the limited number of patients studied and the relatively short follow-up, these results should be interpreted with caution. However, providing the framework for future prospective studies addressing the role of strategies of treatment intensity modulation according to on-treatment prognostic assessment in order to maximize the risk to benefit ratio of HL treatment. While late CTRI may be one of the parameters to consider, these studies will clearly incorporate PET, whose increasing importance in lymphoma patients management has been confirmed by its inclusion among the recently revised response criteria for malignant lymphoma [34].

references

26. Straus DJ, Portlock CS, Qin J et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed be


